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Long-term oncologic outcomes after primary retroperitoneal lymph node dissection: minimizing the need for adjuvant chemotherapy

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Objective:

To analyze the oncological outcomes of men undergoing primary RPLND and characterize the use of adjuvant chemotherapy and template dissections.

Methods:

Retrospective review of Indiana University testis cancer database identified patients who underwent a primary RPLND between 01/2007 and 12/2017. Patients and providers were contacted to obtain information regarding adjuvant therapy, recurrence, and survival. Primary outcome was recurrence-free survival (RFS). Kaplan-Meier curves assessed survival differences stratified by pathologic stage, template of dissection, and use of adjuvant chemotherapy.

Results:

Overall, 274 patients were included. Most men presented with CS-I disease (214, 78%). A modified unilateral template was performed in 257 (94%) and bilateral template in 17 (6%). Overall, 148 (54%) and 126 (46%) of men had Pathologic Stage I (PS-I) and PS-II disease, respectively. Thirteen patients (10%) with PS-II disease were treated with adjuvant chemotherapy. With a median follow-up was 55 months, only 33 (12%) patients recurred. Of the 113 patients with PS-II disease who did not receive chemotherapy, 21 (19%) relapsed and 81% were cured were surgery alone and never recurred. No difference in RFS was noted between modified and bilateral template dissections.

Conclusions:

The use of adjuvant chemotherapy has been minimal over the past decade. The majority (81%) of men with PS-II disease were cured with RPLND alone and were able to avoid chemotherapy. Modified unilateral template dissection provided excellent oncologic control while minimizing morbidity.

Introduction:

Testicular cancer is the most common solid malignancy among young males, accounting for more than 9,000 new cases in United States annually [1, 2]. Nearly 50% of patients with testis masses are diagnosed with non seminomatous germ cell tumors (NSGCT), one third of whom present with clinical stage I (CS-I) disease [3].

Management options of CS-I disease include surveillance, surgical management with a primary retroperitoneal lymph node dissection (P-RPLND), or chemotherapy in the form of 1 cycle of Bleomycin, Etoposide, and Cisplatin (BEP). P-RPLND is generally used to manage CS-I or low-volume CS-II NSGCT and has been shown to be curative in up to 70-90% of patients [4, 5]. Previous institutional series noted that the rate at which patients with initial CS-I are found to have pathologic stage II (PS-II) disease ranges from 19-28% which confers a relapse risk of 20-36% [6]. Adjuvant chemotherapy following RPLND in the form of 2 cycles of Bleomycin, Etoposide, and Cisplatin (BEP) has demonstrated a significant reduction in relapses rates in a randomized clinical trial [7]. However, no difference in overall survival was noted between those treated with adjuvant chemotherapy following RPLND vs. those only treated at the time of relapse. Thus, adjuvant chemotherapy comes at a cost of a significant burden of overtreatment if chemotherapy is given to all patients with PS-II disease. Adjuvant chemotherapy usage for PS-II patients has been as high as 55% in previous open series and 41-100% laparoscopic/robotic series with virtually no recurrence recorded in those men completing therapy [8-16].

Historically, patients opting for surgical management were treated with bilateral template and suprahilar dissections which were associated with some morbidity. With improved cross-sectional imaging, serum tumor markers, and anatomic mapping studies, dissection templates initially began to eliminate supra-hilar dissection [17]. Later modification of the templates allowed for unilateral dissections to limit morbidity and improve rates of antegrade ejaculation while maintaining oncologic control [18].

In this study, we sought to examine the oncological outcomes of men undergoing primary RPLND over the past decade and to describe the use of adjuvant chemotherapy, templates of dissection, and recurrence patterns.

Methods:

Patient Selection:

The prospectively maintained Indiana University testis cancer database was queried to identify men who underwent open primary RPLND for NSGCT between 01/2007 and 12/2017. Patients and referring providers were contacted to obtain information regarding receipt of adjuvant therapy, recurrence, and survival. Patients who could not be contacted or had incomplete information were excluded. The clinical and pathologic stage of those excluded were similar to patients included in the study.

Primary and Secondary Outcomes:

The primary outcome was recurrence-free survival (RFS). Recurrence was defined as development of metastatic disease on axial cross-sectional imaging of the chest, abdomen and pelvis and/or a rise in serum tumor markers with subsequent initiation of combination cisplatin-based chemotherapy. Recurrence-free survival was calculated from the date of the RPLND until the date of recurrence. Patients were censored at the date of last follow up if they did not recur. Secondary outcomes included a description of recurrence patterns, indications for adjuvant chemotherapy and overall survival (OS). RFS stratified by template of dissection, pathologic stage, and receipt of adjuvant chemotherapy was also assessed.

Statistical Analysis:

Descriptive statistics including means and standard deviations (or median and interquartile ranges) were used for continuous variables, while counts and frequencies summarized categorical variables for the entire cohort. Student's t-tests and chi-square tests were used to compare normally distributed continuous

and categorical variables, respectively. Recurrence-free and overall survival was calculated and survival curves were constructed using the Kaplan-Meier method. Stratified recurrence-free survival analysis based on template of dissection and pathological stage/adjuvant chemotherapy receipt was conducted. Differences in survival curves were compared with the log-rank test. All statistical analysis was conducted using SAS 9.4 (SAS Institute, Cary, NC) using an alpha value of 0.05.

Results:

Patient Population and Demographics:

A total of 305 patients underwent a primary retroperitoneal lymph node dissection for NSGCT between 2007 and 2017. Recurrence, follow up, and survival data was obtained for 274 (90%) patients. The median age at presentation was 28 and the vast majority were white (96%). Most men had CS-I disease (214, 78%) whereas 60 (22%) men were CS-II. All men had normal tumor markers preoperatively (AFP and hCG). Laterality of the primary tumor was right in 135 (49%) and left in 139 (51%). Patients with embryonal predominance accounted for 46% and those with lymphovascular invasion (LVI) accounted for 37% of patients. The template of dissection was modified unilateral in 257 (94%) and bilateral in 17 (6%). Reasons for bilateral template dissection included: size of RP mass intraoperatively >2 cm and multifocality of disease (7, 41%), bilateral RP disease (4, 23%), bilateral synchronous primary testicular tumors (3, 18%), variant histology with non GCT components (2, 12%), and unknown (1, 6%). Patient demographics are summarized in Table 1.

Pathological assessment:

Overall, 148 (54%) and 126 (46%) men had pathologic stage I and stage II disease, respectively. Patients with CS-I and CS-II disease were noted to have PS-II disease in 35% and 87% of cases, respectively. Of those with pathologic stage II disease, histologic analysis consisted of mixed or non seminomatous germ

cell tumor (93, 74%), teratoma only (17, 13%), and pure seminoma (16, 13%). Among patients with PS-II disease, the median number of positive lymph nodes was 2. Notably, 13% of CS-II were ultimately found to be PS-I.

Receipt of Adjuvant Chemotherapy:

The majority of patients with pathologic stage II disease were observed with only thirteen patients (10%) treated with adjuvant chemotherapy. The indications for adjuvant chemotherapy were ≥ 5 nodes positive (7, 54%), positive node > 5 cm (2, 15%), and patient preference (4, 31%). None of the 13 patients with pathological stage II disease who received adjuvant chemotherapy recurred. One-hundred and thirteen patients with pathological stage II disease did not receive chemotherapy. The recurrence rate in this cohort was 19% (21 patients) with a median time to recurrence of 3.6 months. Chemotherapy was avoided in 92 men with PS-II disease (81%) who were cured with surgery alone.

Recurrences:

With a median follow-up of 55 months, 33 (12 %) patients recurred. Twenty-one patients were pathologic stage II and 12 patients were pathologic stage I. The median time to recurrence for the total cohort was 3.6 months with 85% of recurrences noted within 1 year of RPLND. The rates of recurrence stratified by pathologic stage and receipt of adjuvant chemotherapy were: PS-I (8%, 12), PS-II without adjuvant chemotherapy (19%, 21), and PS-II with adjuvant chemotherapy (0%, 0). RFS curves stratified by pathologic stage/adjuvant chemotherapy receipt are shown in Figure 1. The 2-year recurrence free survival for PS-I, PS-II without chemotherapy, and PS-II with adjuvant chemotherapy was 92%, 83%, and 100%, respectively. All recurrences were treated successfully with standard first-line chemotherapy.

Of the 33 recurrences, the location of recurrence was biochemical in 7, pulmonary in 9, retroperitoneal only in 6, suprahilar only in 2, mediastinal in 3, and pelvic in 2. Additionally, 1 patient had simultaneous recurrences in both the retroperitoneum and lung, another patient had simultaneous recurrences in the suprahilar region and lung, and 2 patients had recurrence in the brain. No patients developed peritoneal

carcinomatosis or liver metastases. An anatomical description of recurrence location is illustrated in Figure 2. There was no significant difference in recurrence-free survival among patients who had bilateral template (1/17, 6%) or modified unilateral (32/257, 12%) approach.

Seven patients (2.6%) recurred within the retroperitoneum, one of which also had simultaneous lung recurrence. All seven patients had PS-II disease at the time of RPLND. The location of recurrence in these patients consisted of in-field in 3, out-of-field in 4 (contralateral retroperitoneum). Of the 7 retroperitoneal recurrences, 1 had a bilateral template and 6 had a modified unilateral template. Of the 257 patients who had a unilateral modified dissection, only 4 patients (1.6%) recurred in the contralateral retroperitoneum. The overall in-field recurrence rate was 1.1% (3 of 274).

Overall Survival:

A total of 6 patients died during follow-up and only two died from testis cancer. Disease-specific survival (DSS) for the entire cohort was 99.3%. Overall survival (OS) of the total cohort was 97.8%.

When examining the 2 mortalities from testis cancer, one patient had embryonal predominant NSGCT on orchiectomy and was found to be PS-I on RPLND. He later recurred after a delay in presentation with a large tumor burden in the mediastinum, eventually presenting with brain metastasis despite salvage chemotherapy and died. The other patient had embryonal predominant NSGCT on orchiectomy and was PS-I on RPLND. He relapsed 2 years later with brain metastasis consistent with embryonal carcinoma as well as in the chest and small bowel mesentery with pathology consistent with chondrosarcoma and rhabdomyosarcoma transformation. Regarding the remaining 4 mortalities, one patient expired due to a seizure disorder, another due to a motor vehicle accident, another due to complications from alcoholism, and the exact cause of the 1 other was unknown.

Discussion:

Two changes were implemented at our institution over the past decade. The use of modified unilateral template dissections was preferred in contrast to a bilateral template in appropriately selected patients. A left modified template consisted of performing a split and roll technique on the aorta and harvesting the pre-aortic, para-aortic, retroaortic, and left common iliac nodes, while a right modified template involved performing a split and roll technique on the aorta harvesting the pre-aortic, interaortocaval, retro-aortic, paracaval, retrocaval, and right common iliac nodes. Additionally, adjuvant chemotherapy was rarely recommended in patients found to have PS-II disease at the time of RPLND. Despite these changes, we have seen no significant increase in recurrence rates with 33 recurrences recorded over a 10 period (12%). Although adjuvant chemotherapy was given to 10% of patients with PS-II disease, only 19% recurred and all were cured with first-line chemotherapy.

The historical dogma of two cycles of adjuvant chemotherapy for all men with PS-II disease was evaluated in a randomized controlled trial published in 1987. [7] One rationale for this study was to avoid 3-4 cycles of induction cisplatin-based chemotherapy in men with stage II disease due to the acute toxicity of chemotherapy during that time period. Williams et al. randomized men with PS-II disease after primary RPLND to observation or chemotherapy. Recurrence rates were lower in men who received chemotherapy and roughly half of the men who were initially observed recurred and required chemotherapy. The relatively high recurrence rate of 50% in this trial is reflective of including men who had elevated markers at time of surgery, first generation imaging, and a number of men with bulkier disease compared to current studies. Despite the higher recurrence risk in the observation group, the cure rates were similar between the groups. It is our institutional preference to withhold adjuvant chemotherapy in most men to avoid overtreatment of men cured with surgery alone. The rate of adjuvant chemotherapy use for men with PS-II disease in our current study (10%) is much lower than the rates reported in other open (50-55%) [11, 13], laparoscopic (24-100%) [12, 14, 16, 19] and robotic (29-62%) [15, 20] series (Table 2). The majority (81%) of men with PS-II disease who did not receive adjuvant chemotherapy in

our series never recurred. Our lower use of adjuvant chemotherapy limited chemotherapy exposure, and potential long-term toxicity associated with it, to only those men who recur, while having negligible effects on overall survival. Future studies analyzing oncological outcomes of either open or minimally invasive RPLND in the primary setting need to assess the use and perhaps overuse of adjuvant chemotherapy for true comparability of the operative technique. Furthermore, it is important to note that 13% of patients with clinical stage II disease were found to have pathologic stage I disease. This proportion of false "positive" with CS-II disease has previously been demonstrated by Donohue et. al [13]. This would serve as a cautionary note to be wary for patients with CS-II disease and normal markers receiving chemotherapy. We would advise against subjecting such patients to BEPx3 or EPx4 and potential short term and late complications given that they might already be cured with orchiectomy +/- RPLND alone.

The debate regarding the template for dissection for men undergoing primary or post-chemotherapy RPLND is longstanding. Modified template dissections were proposed due to the predictable nature of lymphatic metastasis defined with the assistance of mapping studies in an effort to limit patient morbidity [21, 22]. Proponents of bilateral dissections in all patients argue that modified templates increase the risk of incomplete dissection and subsequent recurrence with need for induction chemotherapy. In a retrospective analysis of 500 patients undergoing bilateral template dissections, Eggener et al reported rates of extra-template retroperitoneal disease in 3-23% of patients depending upon the anatomical boundaries of the modified template [23]. Thus, the authors argue for bilateral template in all patients due to high rates of contralateral disease. The vast majority of patients in our series (94%) underwent a unilateral modified template. Yet with a median follow up of 55 months, the recurrence rate in the contralateral retroperitoneum after unilateral modified template was only 1.6%. Additionally, there were no differences in RFS noted between patients who had a modified unilateral vs. bilateral template. Thus, a meticulous modified template dissection can be safely used to minimize morbidity while maintaining excellent oncologic outcomes in the vast majority of CS-I or low volume CS-II disease.

Our results should be viewed within the context of several limitations. This is a retrospective analysis which can be prone to bias and confounding factors. However, the large study size examining primary RPLND outcomes largely without adjuvant chemotherapy in a contemporary cohort is informative. We were unable to contact every patient identified who underwent a primary RPLND, nonetheless, the vast majority (90%) of patients had complete records regarding follow up, recurrence and survival. Furthermore, patients who were unable to be contacted did not have disproportionate adverse pathology (88% were CS-I and 77% were PS-I). The patient's post-operative oncologic care was not centralized and thus, the rationale and thresholds for offering adjuvant chemotherapy was heterogeneous as demonstrated with the inability to determine why 4 patients received adjuvant chemotherapy. Our oncology team generally works closely with referring oncologists and provides guidance regarding follow up, surveillance and chemotherapy use. Finally, the location and presence of some recurrences were not radiographically reviewed centrally at our institution. This could have introduced some variability in the exact location of the recurrence as we had to rely on radiographic reports from outside institutions for some patients. This was especially prevalent in patients treated prior to 2011 as most institutions discarded radiographic images after being archived for seven years.

These limitations notwithstanding, we find that our data supports the use of surveillance and avoidance of adjuvant chemotherapy for most patients with pathologic stage II disease. The overall cure rate with surgery alone was 81%. Furthermore, despite the high rate of unilateral modified template use, recurrence rates in the contralateral retroperitoneum were minimal (1.6%) and there was no difference in recurrence free survival or overall survival.

References

1. Hayes-Lattin, B., Nichols, C. R.: Testicular cancer: a prototypic tumor of young adults. Seminars in oncology, **36:** 432, 2009
2. Stevenson, S. M., Lowrance, W. T.: Epidemiology and Diagnosis of Testis Cancer. Urol Clin North Am, **42:** 269, 2015
3. Gumus, M., Bilici, A., Odabas, H. et al.: Outcomes of surveillance versus adjuvant chemotherapy for patients with stage IA and IB nonseminomatous testicular germ cell tumors. World J Urol, **35:** 1103, 2017
4. Stephenson, A. J., Sheinfeld, J.: The role of retroperitoneal lymph node dissection in the management of testicular cancer. Urol Oncol, **22:** 225, 2004
5. Sweeney, C. J., Hermans, B. P., Heilman, D. K. et al.: Results and outcome of retroperitoneal lymph node dissection for clinical stage I embryonal carcinoma--predominant testis cancer. J Clin Oncol, **18:** 358, 2000
6. Stephenson, A. J., Sheinfeld, J.: Management of patients with low-stage nonseminomatous germ cell testicular cancer. Curr Treat Options Oncol, **6:** 367, 2005
7. Williams, S. D., Stablein, D. M., Einhorn, L. H. et al.: Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular cancer. N Engl J Med, **317:** 1433, 1987
8. Nicolai, N., Miceli, R., Artusi, R. et al.: A simple model for predicting nodal metastasis in patients with clinical stage I nonseminomatous germ cell testicular tumors undergoing retroperitoneal lymph node dissection only. J Urol, **171:** 172, 2004
9. Hermans, B. P., Sweeney, C. J., Foster, R. S. et al.: Risk of systemic metastases in clinical stage I nonseminoma germ cell testis tumor managed by retroperitoneal lymph node dissection. J Urol, **163:** 1721, 2000
10. Donohue, J. P., Thornhill, J. A., Foster, R. S. et al.: Retroperitoneal lymphadenectomy for clinical stage A testis cancer (1965 to 1989): modifications of technique and impact on ejaculation. J Urol, **149:** 237, 1993
11. Al-Ahmadie, H. A., Carver, B. S., Cronin, A. M. et al.: Primary retroperitoneal lymph node dissection in low-stage testicular germ cell tumors: a detailed pathologic study with clinical outcome analysis with special emphasis on patients who did not receive adjuvant therapy. Urology, **82:** 1341, 2013
12. Cresswell, J., Scheitlin, W., Gozen, A. et al.: Laparoscopic retroperitoneal lymph node dissection combined with adjuvant chemotherapy for pathological stage II disease in nonseminomatous germ cell tumours: a 15-year experience. BJU Int, **102:** 844, 2008
13. Donohue, J. P., Thornhill, J. A., Foster, R. S. et al.: The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). J Urol, **153:** 85, 1995
14. Neyer, M., Peschel, R., Akkad, T. et al.: Long-term results of laparoscopic retroperitoneal lymph-node dissection for clinical stage I nonseminomatous germ-cell testicular cancer. J Endourol, **21:** 180, 2007
15. Pearce, S. M., Golan, S., Gorin, M. A. et al.: Safety and Early Oncologic Effectiveness of Primary Robotic Retroperitoneal Lymph Node Dissection for Nonseminomatous Germ Cell Testicular Cancer. Eur Urol, **71:** 476, 2017
16. Nelson, J. B., Chen, R. N., Bishoff, J. T. et al.: Laparoscopic retroperitoneal lymph node dissection for clinical stage I nonseminomatous germ cell testicular tumors. Urology, **54:** 1064, 1999

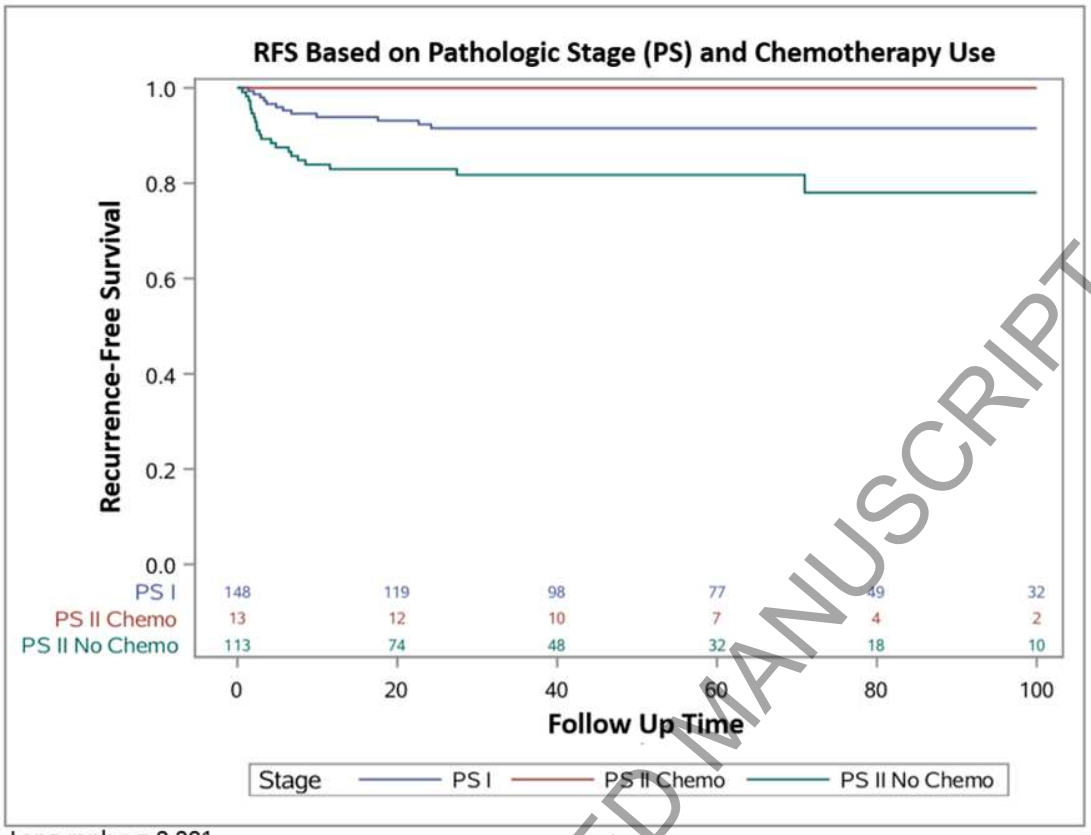
17. Masterson, T. A., Cary, C.: The Use of Modified Templates in Early and Advanced Stage Nonseminomatous Germ Cell Tumor. Adv Urol, **2018:** 6783147, 2018
18. Donohue, J. P., Foster, R. S., Rowland, R. G. et al.: Nerve-sparing retroperitoneal lymphadenectomy with preservation of ejaculation. J Urol, **144:** 287, 1990
19. Nicolai, N., Tarabelloni, N., Gasperoni, F. et al.: Laparoscopic Retroperitoneal Lymph Node Dissection for Clinical Stage I Nonseminomatous Germ Cell Tumors of the Testis: Safety and Efficacy Analyses at a High Volume Center. J Urol, **199:** 741, 2018
20. Rocco, N. R., Stroup, S. P., Abdul-Muhsin, H. M. et al.: Primary robotic RLPND for nonseminomatous germ cell testicular cancer: a two-center analysis of intermediate oncologic and safety outcomes. World J Urol, 2019
21. Weissbach, L., Boedefeld, E. A.: Localization of solitary and multiple metastases in stage II nonseminomatous testis tumor as basis for a modified staging lymph node dissection in stage I. J Urol, **138:** 77, 1987
22. Donohue, J. P., Zachary, J. M., Maynard, B. R.: Distribution of nodal metastases in nonseminomatous testis cancer. J Urol, **128:** 315, 1982
23. Eggener, S. E., Carver, B. S., Sharp, D. S. et al.: Incidence of disease outside modified retroperitoneal lymph node dissection templates in clinical stage I or IIA nonseminomatous germ cell testicular cancer. J Urol, **177:** 937, 2007

	No. of Pts (%)
Primary Testis Mass	
Right	135 (49.3)
Left	139 (50.7)
Embryonal Predominant	126 (46.0)
LVI Present	101 (36.9)
Clinical stage	
Stage I	214 (78.1)
Stage II	60 (21.9)
Template of dissection	
Left modified	132 (48.2)
Right modified	125 (45.6)
Bilateral	17 (6.2)
Pathologic stage	
Stage I	148 (54.0)
Stage II	126 (46.0)
Adjuvant chemo for PS II	
Yes	13 (10.3)
No	113 (89.7)
Recurrence	
PS I	12 (8.1)
PS II without adjuvant chemo	21 (18.6)
PS II with adjuvant chemo	0 (0)

Table 1: Clinical and pathological characteristics

Author	Approach	Year of Publication	Study Period	No. PS II Patients	Adjuvant Chemo Rate
Donohue	Open	1995	1965 - 1989	108	55%
Al-Ahmadie	Open	2013	1989 - 2002	183	50%
Nelson	Laparoscopic	1999	1992 - 1998	29	41%
Neyer	Laparoscopic	2007	1992 - 2005	25	100%
Cresswell	Laparoscopic	2008	1992 - 2007	19	100%
Nicolai	Laparoscopic	2017	2000 - 2014	29	24%
Pearce	Robotic	2017	2011 - 2015	8	62%
Rocco	Robotic	2019	2008 - 2019	17	29%

Table 2: Adjuvant chemotherapy usage rates among patients with PS II



Long-rank p = 0.001

Figure 1: Recurrence free survival (RFS) stratified by pathologic stage and chemotherapy use

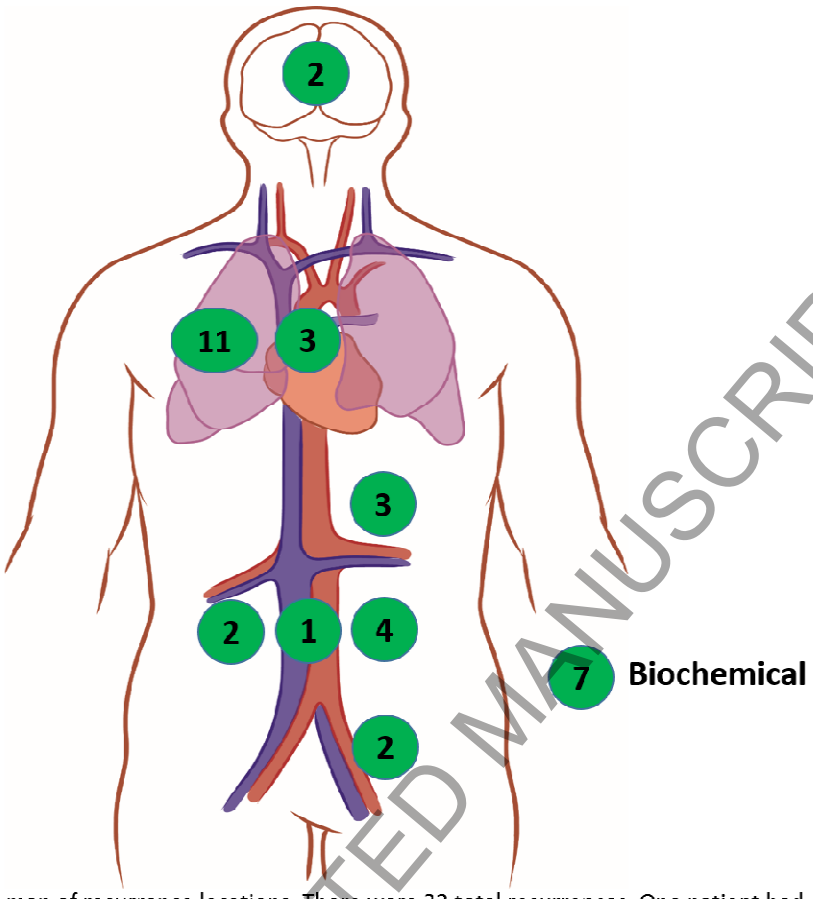


Figure 2: Anatomic map of recurrence locations. There were 33 total recurrences. One patient had simultaneous recurrences in the lungs and retroperitoneum, another in the lungs and suprahilar region.